Green Chemical Environ-Economic Synthesis of Some O, N and S Containing Bioactive Heterocyclic Compounds

A PROPOSED RESEARCH PLAN IN PARTIAL FULFILMENT FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN
SCIENCE

OF

MODY INSTITUTE OF TECHNOLOGY & SCIENCE

Supervisor
Dr. Harshita Sachdeva

Submitted by
Rekha Saroj

Faculty of Engineering & Technology
MODY INSTITUTE OF TECHNOLOGY & SCIENCE
(Deemed University u/s 3 of the UGC Act 1956)
Lakshmangarh-332311, District Sikar,
Rajasthan (India)

CONTENTS

	Page No.
1. INTRODUCTION	1
2. PURPOSE OF STUDY	2
3. REVIEW OF LITERATURE	3
4. PROPOSED WORK	5
5. WORK ALREADY DONE	6
6. METHODOLOGY	9
7. RESULTS OBTAINED	11
8. CONCLUSION	12
9. REFERENCES	12

Green Chemical Environ-Economic Synthesis of Some O, N and S Containing Bioactive Heterocyclic Compounds

1. Introduction

Green chemistry is the new and rapid emerging field of chemistry. Its growing importance is in utilization of maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. It incorporates a new approach to the synthesis, processing, and application of chemical substances in such a manner as to reduce threats to health and environment. This new approach is also known as Environmentally Benign Chemistry, Atom Economy, Benign by Design Chemistry, and Sustainable Chemistry.[1-3] It is one of the best alternatives for traditional chemical synthesis process.[4, 5] It is the design of chemical products and process that reduce byproducts, waste produced and lowering of energy costs but also in the development of new methodologies.[6] Green technologies are one of the highest priorities for today's chemists. It provides a technical solution to many environmental problems.

The most important goal for chemists is to ensure that the next generation of synthetic protocols for drugs and fine chemical synthesis is more sustainable, fully protected for human health and environmental protection, easily recycled reagent and fully greener than the current generation. Areas for the development of green chemistry include use of alternative feedstock, use of innocuous reagent, employing natural process, developing alternative reaction condition, minimizing energy consumption, use of alternative solvents.[7] Among the challenges for chemists include discovery and development of novel and simple environmentally safe chemical processes for selective synthesis by identifying alternative reaction condition and solvent for much improved selectivity, energy conservation and less or non toxic, waste generation and inherently safer chemical products.[8]

Heterocyclic compound is one, which posses a cyclic structure with at least two different type of hetero atoms in the ring. Nitrogen, Oxygen, and Sulphur are the most common heteroatom.[9] These compounds are very widely distributed in nature and are essential for life in various ways. Most of the sugars and their derivatives, including vitamin C, for instance, exist in the form of five-member (furan)[10] or six-member (Pyran)[11,12] rings containing one oxygen atom. Most of the members of vitamin B group possess heterocyclic ring containing nitrogen. One

example is vitamin B6 (pyridoxine),[13] which is a derivative of pyridine, essential in amino acid metabolism.[14]

The chemistry of the carbon-nitrogen double bond plays a vital role in the progresses of chemistry science. Schiff-base compounds have been used as fine chemicals and medical substrates. Recently, Schiff bases have been expanded enormously and embraced wide and diversified subjects comprising vast areas of organic compounds.[15] They are first reported by Hugo Schiff in 1864.[16] They are condensation products of ketones or aldehydes with primary amines and formation of Schiff base generally takes place under acidic or basic condition or in the presence of heat. They are used as starting material for the synthesis of various bioactive heterocyclic compounds. They are also used as intermediate for the synthesis of amino acids (or as ligands for preparation of metal complexes). They behave as a flexi dentate and commonly coordinate through the O-atom of the deprotonated phenolic group and N-atom of azomethine.[17-19]

In chemistry, Schiff bases find versatile use. Some of them are the basic units in certain dyes, some are used as liquid crystals.[20] In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. They show wide variety of biological activities like anticancer[21], anticonvulsant[22], antibacterial, antifungal[23], antituberculosis[24], insecticidal, plant growth inhibitors, etc. Their wider applications and diverse potential biological activities promoted us to synthesize new Schiff base containing heterocyclic moiety under environmentally benign reaction conditions and to screen them for various biological activities.[25]

2. PURPOSE OF STUDY

In these environmentally conscious days, one of the main challenges to the chemical research has been to develop 'Clean and Efficient' technologies for chemical synthesis.[26] The developments in technology are directed towards environmentally sound and cleaner procedures[27].

Hence, the present day's chemists are no longer confined to using only thermal energy for driving chemical reactions. With increasing complexity of use problems and the availability of newer method of activation of chemical reactions, chemists have resorted to use wide variety

of techniques such as photochemical, electrochemical, microwave and enzymatic methods. With the easy availability of "Grindstone Technology", [28, 29] their popularity and synthetic utility in organic chemistry have increase considerably in recent years. Because this technology is simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favorable procedure in organic chemistry. So we have studied the use of **"Grindstone Technology"** as improved tools in process chemistry and organic synthesis.[30, 31]

Further, Encouraged by the vast potential of "Grindstone Technical Organic Synthesis" and wide variety of biological activities associated with O, N and S containing heterocycles, the envisaged work has been undertaken as **"Green Chemical Environ-Economic Synthesis of Some O, N, and S Containing Bioactive Heterocyclic Compounds"**

3. Review of literature

In order to achieve the "triple bottom line" we need to develop new, more environmentally friendly, chemical products and process. Catalysis which has played a vital role in the success of the industry also played a very important role in the new greener industry of the new Century. It not only helps in green chemical processes but also reduces the environmental impact of processes and reduces the cost of the processes.[32, 33]

Development of new synthetic processes with high efficiency, high eco-chemical property and environmentally friendly nature is one of the most important subjects not only for basic research but also for industries. We are approaching this problem using "molecular catalyst" i.e. transition metal catalyst[34] and Lewis acids catalyst.[35] Lewis acid catalysts have been of great interest in organic synthesis while various kind of Lewis acid promoted reaction have been developed and many have been applied in chemistry. So far many Lewis acid catalysts has been applied in the synthesis of dihydropyrimidinones[36] but they suffer from various drawbacks.[37-39]

In this context, I have synthesized large number of O, N and S containing heterocyclic compounds in the presence of transition metal halides as Lewis acid catalyst using Grindstone Chemistry Technique. In continuation to our earlier interest in the synthesis of heterocyclic compounds under the frame work of green chemistry, we have developed a quick,

environmentally, safe non-toxic, economic and clean synthesis called "Grinding". It is one of the green chemistry techniques in which reactions are initiated by just grinding the reaction together with transfer of very small amount of energy through friction. It also results in high reactivity and less waste products. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecofriendly favorable procedure in chemistry.

In this proposal, I have summarized our activity in the area of greener synthetic transformations which use grindstone technology, microwave irradiation under solvent free condition or using aqueous medium or supported reagents or using Lewis acid catalysts for the synthesis of some O, N, and S containing bioactive heterocyclic compounds.

NITROGEN-CONTAINING HETEROCYCLES

Nitrogen heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds.[40, 41] Triazoles are another important class of nitrogen heterocycles, and specifically, the 1, 2, 4-triazole nucleus has been found to be an integral part of therapeutically interesting compounds that display significant antibacterial, central nervous system (CNS) stimulative, sedative, antifungal, and antitumor activities.[42-44] Consequently, the synthesis of this heterocyclic nucleus has gained great importance in organic synthesis.

OXYGEN-CONTAINING HETEROCYCLES

Oxygen heterocycles are important classes of building blocks in organic synthesis, and several derivatives of these oxygen heterocycles have attracted much attention of medicinal chemists over the years. Tetrahydropyrans are prevalent subunits in an assortment of natural products including carbohydrates, polyether antibiotics, and marine toxins.[45]

SULFUR-CONTAINING HETEROCYCLES

Sulfur heterocycles are also important classes of heterocycles in pharmaceuticals and organic synthesis, which are known to possess important biological properties and have attracted much attention of medicinal chemists over the years. In view of their cyclooxygenase-inhibitory activity, thiazoles find application viz therapy as thromboembolic agents and are of significant importance being an integral structural component of vitamin B1 and coenzyme carboxylase.[46]

4. PROPOSED WORK

The present work entitled **"Green Chemical Environ-Economic Synthesis of Some O, N and S Containing Bioactive Heterocyclic Compounds"** would be carried out with the aim to explore newer trends in the upcoming areas of "Green chemistry" by using Grindstone technology for devising alternative, clean, efficient, economic and environmentally benign methodology.

The present work will be carried out in following two parts.

(A) Synthesis

(B) Biological Screening

(A) Synthesis :

Among the most promising ways to reach this goal, solvent free techniques hold a strategic position as solvents are often very toxic, expensive, and problematic to use and to remove. It is the main reason for development of such modern technologies. I propose to investigate the following research plan to synthesize some biologically active heterocyclic compounds.

1. Investigation of the reaction of substituted aromatic aldehyde, β-ketoester with urea/thiourea/substituted thiourea in the presence of various Lewis acid catalysts using Grindstone technology: Improved synthesis of Biginelli compounds.
2. Investigation of the reaction of substituted 1H-indole-2, 3-dione and various amino-acids with thiosemicarbazide/substituted thiosemicarbazide: synthesis of novel Schiff base derivatives containing oxindole and thiadiazole moieties.
3. Investigation of the reaction of substituted aromatic aldehydes and substituted amino acids with thiosemicarbazide/ substituted thiosemicarbazide: Synthesis of Schiff base derivatives containing triazole moiety.
4. Investigation of the reaction of substituted 1H-indole-2, 3-dione with organic acids

(B) Biological Screening of the compounds:

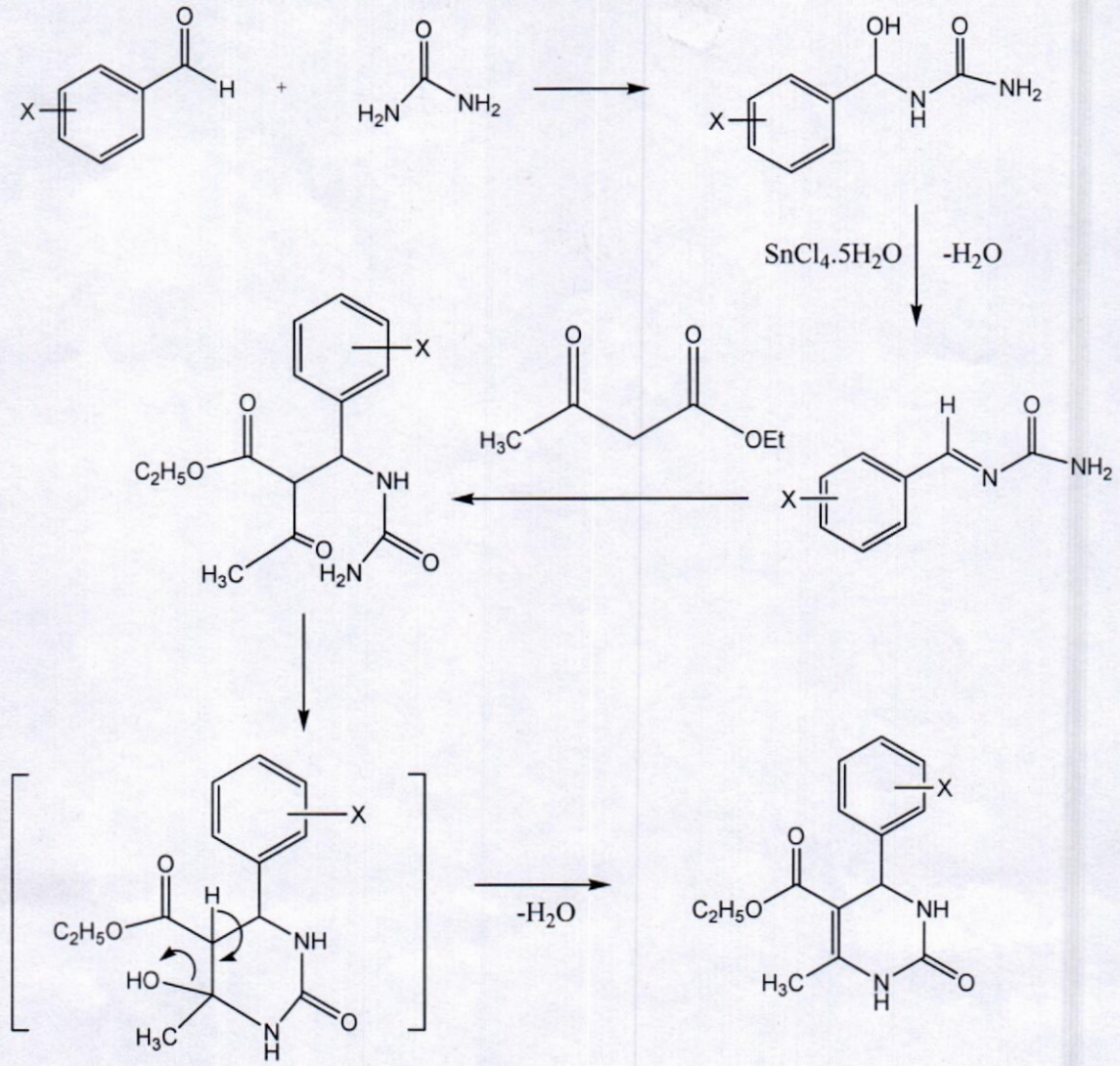
A representative number of compounds will be screened for anti-fungal and anti-bacterial activities in Department of Microbiology, MDS University, Ajmer, Rajasthan and anti-cancer activity in "Advanced Centre for Treatment, Research and Education in Cancer (ACTREC)" Kharghar, Navi Mumbai.

1. **Antifungal activity-** Compounds will be screened for antifungal activity againstAspergillus sp., Penicillum sp., Fusarium oxy., Alterneria bracicicol, Chetorium orium and Glycopodium sp.
2. **Antibacterial activity-** Compounds will be screened for antibacterial activity against Pseudomonas aeruginosa, Bacillus licheniformis, Micrococcus luteus, Staphylococcus aureus and Esherichia coli.
3. **Anticancer activity-** Compounds will be screened for anti cancer activity against the Various human cell lines like "Human Colon (Colo-205)".

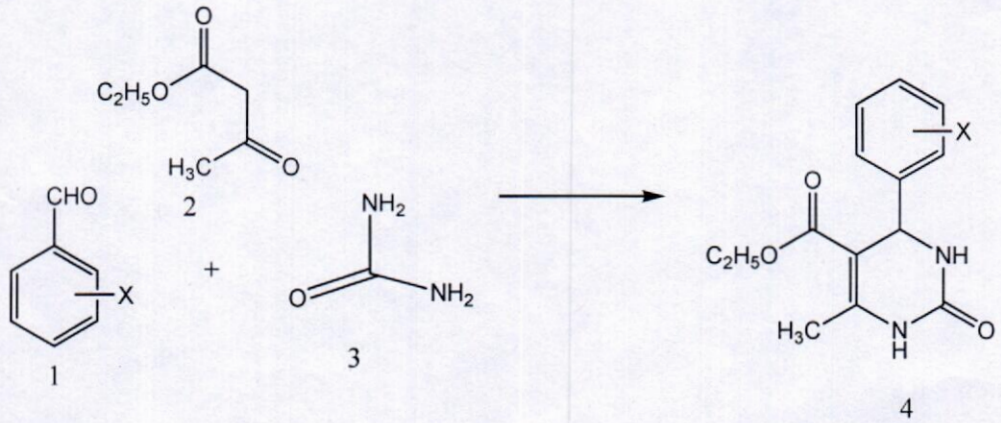
5. WORK ALREADY DONE

1. **Comparative studies of Lewis Acidity of substituted tin chlorides in Multicomponent Biginelli Condensation by using Grindstone Technology.**

As per ongoing efforts to synthesize privileged class of compounds and exploiting the Inherent capacity of biginelli reaction to be promoted by acids, I have reported simple and effective modification of Biginelli reaction that produces high Yields of DHPM's using catalytic amount of $SnCl_4.5H_2O$ while preserving the original one pot strategy under solvent free conditions using Grindstone Technique. Further, comparative efficiency of $SnCl_4.5H_2O$ /mono/di/tri butyl tin chloride, $HgCl_2$, and $SnCl_2$ to catalyze Biginelli condensation reaction is also studied using Grindstone Chemistry Technique.



Mechanism



SchemeI-Reagents and conditions: $SnCl_4$/$RSnCl_3$/R_2SnCl_2/ R_3SnCl, $SnCl_2$, $HgCl_2$, grinding

X=H,4-OCH_3;4-OH;4-Cl;3-OCH_3;2,4-Dimethyl;3-OH,4-OCH_3;3-OCH_3,4-OH;3,4-dimethoxy; 2-OH;2-Cl;3-NO_2;3,4,5-trimethoxy

In the present investigation, tin chloride is found to be superior catalyst over other three mono/ di / tri butyl tin chlorides both in terms of yields and purity of Biginelli compounds. It is found that $SnCl_4.5H_2O$ works as an excellent catalyst for the one-pot, three-component and solvent free synthesis of DHPM's. This procedure is simpler (preserving the one pot synthesis), economical, milder, faster, and is also consistent with the green chemistry theme since no solvent is needed and affords excellent yields.

2. Investigation of the reaction of substituted 1H-indole-2, 3-dione and various amino acids with thiosemicarbazide/ substituted thiosemicarbazide: Synthesis of novel Schiff base derivatives containing oxindole and thiadiazole moieties.

I propose to investigate the formation of Schiff base derivatives in aqueous medium by the condensation of substituted oxo-indol-3-ylidene-amino carboxylic acid **(3)** with thiosemi carbazide **(4)** in phosphorus oxychloride. Intermediate **(3)** has been synthesized by the Knovengeal condensation of substituted indol-2, 3-dione **(1)** with a series of substituted amino acids.

3. Investigation of the reaction of substituted aromatic aldehydes and substituted amino acids with thiosemicarbazide: Synthesis of Schiff base derivatives containing triazole moiety.

I propose to investigate the aqua mediated facile synthesis of Schiff base derivatives by the condensation of substituted oxo-indol-3-ylidene-amino carboxylic acid **(3)** with thiosemicarbazide **(4)**. Intermediate **(3)** has been synthesized by the Knovengeal condensation of substituted aldehydes **(1)** with a series of substituted amino acids **(2)**.

6. METHODOLOGY

I have used following methods for the synthesis of some biodynamic heterocyclic compounds:

(A) Grindstone Technology.

(B) Conventional method.

(C) Aqua mediated Synthesis.

(D) Microwave using H_2O and ethylene glycol.

(A) Grindstone Technology

This method is an improvement over traditional method of organic synthesis which involves the use of non toxic solvent, low heating power, less hazardous Synthetic methodology. Such type of reaction is simple to handle, reduce pollution, efficient, more ecofriendly, economic, interesting, extremely simple, suitable, fast, novel, quick, clean up method, and ecological favorable procedure for synthesis of products.[27, 28]

Grinding does not require solvents leading to safe and environmental friendly synthesis because the solvent-free reaction condition is an important object of green chemistry. Furthermore, the proposed technique does not require external heating or cooling at any stage, leading to energy efficient synthesis providing high yields of products. Generally, Solid-state reactions occur more efficiently and more selectively than does the solution reaction, since molecules in the crystals are arranged tightly and regularly.[31]

(B) Conventional Method

In this method reactions are completed by refluxing on various activation modes like water bath, heating mantle, oil bath, magnetic stirrer etc. Different types of solvents are required for this method like Ethanol, Methanol, Toluene, Dioxane, Benzene, Ethyl acetate, etc. and external power is also required for certain time. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious procedures which result in higher cost of process and the excessive use of solvents, reagents leads to environmental pollution.

(C) Aqua mediated Synthesis

Water is ideally suited for this purpose owing to its non-toxic character. Its enormous abundance on this planet makes water a readily accessible alternative. There are also advantages from an economic point of view. Under microwave irradiation water is rapidly

heated to high temperatures, enabling it to act as a less polar pseudo-organic solvent. Moreover, precise control of the reaction temperature is easily achieved because of the very high heat capacity of water.[47]

Water is perhaps one of the greener solvents one can imagine in terms of costs, availability, safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow and Grieco in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. For instance, the rate and stereo-selectivitity of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic co-solvents or surfactants helps to increase the solubility of non polar reactants in water by disrupting the strong hydrogen-bond network of pure water. The discovery that Lewis acids, especially some metal triflates, can efficiently catalyze reactions in water also contributed to popularize it as solvent in organic reactions.[48, 49]

Many interesting examples of organic reactions in water have appeared recently in the literature, from which we selected a few representative of the great potential of water as solvent.

(D) Microwave Induced Synthesis

The solvent free microwave-assisted organic reactions can be broadly categorized into two types:

(I) Reactions on solid mineral supports in dry media

This technique was initially described by Keinan and Mazur. Mineral oxides are often very poor conductors of heat but behave as very efficient microwave absorbents, this resulting in turn in a very rapid and homogeneous heating. Consequently, they display very strong specific microwave effects with significant improvements in temperature homogeneity and heating rates enabling faster reactions and less degradation of final products when compared to classical heating.[50-52]

Aluminas, Silicas, Clays, Zeolites or Envirocates EPZG and EPZ 10 selected as acidic or basic supports[53, 54] depending on the type of organic reaction. Alumina alone can possibly act as a

base towards a rather acidic molecule but if a strong base is necessary, KF on alumina[55] can ionize carbon acidic up to pka~35.

Montmorillonites (clays) such as K10 and KSF offer acidities very close to nitric or sulphuric acids. Envirocates EPZG and EPZ 10 are solid supported catalysts which have Bronsted and Lewis acid characteristics where as EPIC is solid supported strong Bronsted acids, some of the supported reagents, namely clay-supprted iron (III) nitrate (clayfen and copper (II) nitrate (claycop) will also be prepared.

(II) Reaction using neat reactants

These are heterogeneous reactions without any catalyst or support. The simple heterogeneous mixture of the neat reactants can eventually lead to a reaction in which either the solid is partially soluble in the liquid with a reaction occurring in the liquid phase or the liquid is absorbed on to the surface of the solid with a reaction occurring at the interface. In both situations, the presence of solvent is deleterious due to dilution of the reactants. However, we have developed the facile neat reactions under microwave even if all the reactants are solid.

1. RESULTS OBTAINED

Two Series have been completed and published in the form of research papers.

(A) Papers Published in Journals

1. Comparative studies of Lewis Acidity of Alkyl-Tin Chlorides in Multicomponent Biginelli Condensation using Grindstone Chemistry Technique. **J. Chil. Chem. Soc. 2012, 57, 1012-1016.**

2. $HgCl_2$ promoted one pot synthesis of 3, 4-dihydropyrimidin-2 1*H*)-ones and thiones under solvent free conditions. **Heterocyclic Letters, 2011, 1(4), 297-304.**

(B) Papers presented/published in conferences

1. Green-chemical Lewis-Acid Catalyzed Biginelli Reaction "National Seminar on *role of Green Chemistry for risk free environment"* 2010, Poornima group of college, Jaipur (Raj.) 18th Dec.
2. Green-chemical Lewis-Acid Catalyzed Facile synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones. "3rd International Conference on HETEROCYCLIC CHEMISTRY ICHC" 2011, Rajasthan University, Jaipur.

3. Green-chemical Lewis-Acid Catalyzed Biginelli Reaction. "The 48th Annual Convention of Chemists" organized by the Indian Chemical Society and hosted by the Department of Chemistry, University of Allahabad. 2011,
4. One-Pot Multi-Component Lewis Acid Catalyzed Biginelli synthesis using Grindstone Chemistry Technique. "International Conference on *Green Chemistry* (ICGC)-2011", Central University of Rajasthan, Kishangarh.

1. CONCLUSIONS

Synthesized compounds were screened for antibacterial activity against bacteria *Pseudomonas aeruginosa, Bacillus licheniformis, Micrococcus luteus, Staphylococcus aureus,and Esherichia coli,* by the Agar Well Diffusion method. Most of the compounds were found to be active against bacteria *Bacillus, E coli, M luteus* at 500µg / ml concentration. Compounds were also screened for antifungal activity against Aspergillus sp, Penicillum sp, Fusarium oxy. Alterneria bracicicol, Chetorium orium, and Glycopodium sp. by measuring the zone of inhibition in mm. The antimicrobial activity was performed by cup plate method at concentration 500 µg / ml and 250 µg / ml and some compounds were found to be active against A. *alterneria, fasurium oxy.*

References

1. Anastas, P. T. & Beach, E. S. Green Chemistry: The Emergence of a Transformative Framework. *Green Chemistry Letters and Reviews* **2007**, 1, 9-24.
2. Ahluwalia, V. K.; Kidwai, M. "New Trends in Green Chemistry." Anamaya publisher New Delhi, 2nd edition **2007**, 5-18, 250.
3. Manley, J. B.; Anastas, P. T. & Cue, B. W. Frontiers in Green Chemistry: meeting the grand challenges for sustainability in R&D and manufacturing *Journal of Cleaner Production* **2008**, *16*, 743-750.
4. Choo, J. L. and Trost, B. M. Green Chemistry for chemical synthesis PNAS **2008**, 105 (36), 13197-13202.
5. Warren, L.; Emily. Green Chemistry: Scientists Devise New "Benign by Design" Drugs, Paints, Pesticides and More. *Scientific American* **2010**, 28.
6. Tanaka, K. Solvent free organic synthesis. *Green Chemistry, Wiley-VCH* **2011**.
7. Patti, A. "Green approaches to asymmetric catalytic synthesis." **2011**, 140.

8. Polshettiwar, V.; Varma, R. S. Green chemistry by nano-catalysis. *Green Chemistry* **2010**, 12 (5), 743-754.
9. Landge, S. M. Synthesis of Condensed Benzo N, N- Heterocycles by Microwave-Assisted Solid Acid Catalysis. *Catal. Lett.* **2008**, 122, 338-343.
10. Polshettiwar, V. and Varma, R. S. Greener and expeditious synthesis of bioactive heterocycles using microwave irradiation. *Pure Appl. Chem.* **2008**, 80, 777–790.
11. Petrov, V. A. "Fluorinated heterocyclic compounds: synthesis, chemistry and Result *Science"* **2009**, 515.
12. Salvador, J. A. R.; Ppinto, R. M. A.; Silvestre S.M. Recent advances of bismuth (III) salts in organic chemistry: application to the synthesis of heterocycles of Pharmaceutical interest. *Curr Org Synth.* **2009**, 6, 426–470.
13. Brendel, J.; Englert, H. C.; Peukert, S.; Wirth, K.; Wagner, J.; Ruxer, M. Fabienne pilorge substituted heterocycles, their use as medicament, and pharmaceutical preparations comprising them patent number 07825264, **2010**.
14. Glasnov, T. N.; Kappe, C. O. Continuous-flow syntheses of heterocycles. *Journal of Heterocyclic Chemistry* **2011**, 48 (1), 11-30.
15. Jarrahpour, A.; Khalili, D.; Clercq, De. E.; Salmi, C.; Brunel, M. J. Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of Isatin and their derivatives. *Molecules* **2007,** 12, 1720-1730.
16. Ibrahim, M. N. and Sharif, S. A. Synthesis, Characterization and Use of Schiff Bases as Fluorimetric Analytical Reagents. *E-Journal of Chemistry* **2007**, 4, 531-535.
17. Wadher, S. J.; Karande, N.A.; Borkar, D.S. and Yeole, P.S. Synthesis and biological evaluation of schiff bases of cinchophen as antimicrobial agents *International Journal of Chem Tech Research* **2009**, 1, 1297-1302.
18. Satyanarayana, V. S. V; Sreevani, P.; Sivakumar, A. and Vijayakumar, V. Synthesis and antimicrobial activity of new Schiff bases containing coumarin moiety and their spectral characterization. *ARKIVOC* **2008,** 221-23.
19. Amanullah1, M.; Sadozai1, S. K.; Rehman, W.; Hassan, Z.; Rauf1, A. and Iqbal, M. Cytotoxic, antibacterial activity and physico-chemical properties of some acid catalyzed Schiff bases. *African Journal of Biotechnology* **2011**, Vol. 10 (2), 209-213.
20. Khalil, R. A.; Jalil, A. H. and Abd-Alrazzak, A. Y. Application of a Schiff Base Derived from Sulfanilamide as an Acid-Base Indicator. *J. Iran. Chem. Soc.* **2009**, 6, 345-352.
21. Vine, K. L; Locke, J. M.; Ranson, M.; Pyne, S. G.; Bremner, J.B. In vitro cytotoxicity evaluation of some substituted Isatin derivatives. *Bioorg. Med. Chem.* **2007**, 15, 931-938.

22. Smitha, S.; Pandeya, S. N.; Stables, J. P.; Ganpathy, S. Anticonvulsant and sedative-hypnotic activities of N-acetyl/methyl Isatin derivatives. *Sci. Pharm.* **2008,** 76, 621-636.

23. Patel, A.; Bari, S.; Telele, G.; Patel, J.; Sarangapani, M. Synthesis and Antimicrobial activity of some new Isatin derivatives. *Iran. J Pharm. Sci.* **2006,** 4, 249-254.

24. Fadi, A. T.; Bin-Jubair, F. A. S. Antitubercular activity of Isatin derivatives. *Int. J. Res. Pharm. Sci.* **2010,** 1, 113-126.

25. Salimon, J. and Salih, N. New Schiff bases derivatives containing anthracene and 1, 3, 4-thidiazole moieties: Synthesis and fungicidal activity. International Journal of *Pharm.Tech. Research* **2010**, .2, 205-208.

26. Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakaraborty, G. and Manhas, M.S. A simplified green chemistry approach to the Biginelli reaction using 'Grindstone Chemistry'. *Tetrahedron Letters* **2004**, 45, 8351-8353.

27. Vibhute, A.Y.; Mokle, S. S.; Nalwar, Y. S.; Vibhute, Y.B. and Vasant, M. An Efficient and Operationally Simple Synthesis of Some New Schiff Bases Using Grinding Technique. *Bulletin of the Catalysis Society of India* **2009,** 8, 164-168.

28. Zangade, S.; Mokle, S.; Vibhute, A.; Vibhute, Y. An Efficient and Operationally Simple Synthesis of Some New Chalcones by Using Grinding Technique. *Chemical Sciences Journal* **2011,** CSJ-13.

29. Saikia, L.; Maheawari, B. and Jyoti T. A. A rapid, convenient, solventless green approach for the synthesis of oxime using grindstone chemistry. *J. Org. Med. Chem. Lett.* **2011**, 1, 12.

30. Dua, Rajiv.; Shrivastava, S.; Sonwane, S. K. and Srivastava, S.K. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review *Advances in Biological Research* **2011,** 5, 120-144.

31. Saikia1, L.; Maheswari, J. and Thakur J. A rapid, convenient, solventless green approach for the synthesis of oxime using grindstone chemistry. *Organic and Medicinal Chemistr Letters* **2011**.

32. Chary, M. V.; Keerthysri, N. C.; Vupallapati, S. V. N.; Lingaiah, N.; Kantevari, S. Tetrabutylammonium bromide (TBAB) in isopropanol: An efficient, novel, neutral and recyclable catalytic system for the synthesis of 2,4,5- trisubstituted imidazoles, *Catalysis Communications* **2008,** 9, 2013-2017.

33. Sangshetti, J. N.; Kokare, N. D.; Kotharkar, S. A.; Shinde, D. B. Sodium bisulfite as an efficient and inexpensive catalyst for the one-pot synthesis of 2,4,5-triaryl-1H-imidazoles from benzil or benzoin and aromatic aldehydes. Monatshefte Fur Chemie. **2008,** 139, 125-127.

34. Shitole, N. V.; Shelke, K. F.; Sonar, S. S.; Sadaphal, S. A; Shingate, B. B.; Shingare, M. S. L-Pralines as an efficient catalyst for the synthesis of 2, 4, 5-triaryl-1H-imidazoles. *Bulletin of the Korean Chemical Society*, **2009**, 30 (9), 1963-1966.

35. Marcelo, V.; Marques, M. M.; Ruthner, L. F. and Dennis, R. Metall Chloride Hydrates as Lewis Acid Catalysts in Multicomponent Synthesis of 2, 4, 5-Triarylimidazoles or 2, 4, 5-Triaryloxazoles. *J. Braz. Chem. Soc.* **2012,** 23, 171-179.

36. Wilson, K. and Clark, J. H. A special topic issue on green chemistry. Solid acids and their use as environmentally friendly catalysts in organic synthesis. *Pure Appl. Chem.* **2008**, 7, 72.

37. Clark, H. J. Catalysis for green chemistry. *Pure Appl. Chem.* **2001**, 73, 103-111.

38. Landge, S. M.; Synthesis of Condensed Benzo N, N- Heterocycles by Microwave-Assisted Solid Acid Catalysis. *Catal. Lett.* **2008**, 122, 338-343.

39. Bahrami, K.; Khodaei, M. M.; Nejati, A. One-pot synthesis of 1, 2, 4, 5-tetrasubstituted and 2, 4, 5-trisubstituted imidazoles by zinc oxide as efficient and reusable catalyst. *Monatshefte Fur Chemie*, **2011**, 142, 159-162.

40. Padwa, A; Bur, S. Pummerer reaction methodology and strategy for the synthesis of heterocyclic compounds *Chem. Rev*. **2004,** 104, 2401-32.

41. Y. Ju, R. S. Varma. Microwave assisted cyclocondensation of hydrazine derivatives with alkyl dihalides or ditosylates in aqueous media : syntheses of pyrazole, prrazolidine derivatives. *Tetrahedron Lett.* **2005,** 46, 6011.

42. Y, Ju, R. S. Varma An Efficient and Simple Aqueous N-Heterocyclization of Aniline Derivatives:□ Microwave-Assisted Synthesis of *N*-Aryl Azacycloalkanes. *Org. Lett.* **2005,** 7, 2409.

43. Y, Ju. Y.; Varma, R.S. Aqueous N-Heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-Assisted Syntheses of *N*-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives. *J. Org. Chem.* **2006,** 71, 135-141.

44. Demirayak, S.; Benkli, K.; Guven. K. Synthesis and antimicrobial activities of some 3-arylamino-5-[2-(substituted 1-imidazolyl) ethyl]-1, 2, 4-triazole derivatives. *Eur. J. Med. Chem.* **2000, 35**, 1037.

45. C. C. K. Keh, V. V. Namboodiri, R. S. Varma, C.-J. Li. Direct formation of tetrahydropyranols via catalysis in ionic liquid. *Tetrahedron Lett.* **2002, 43**, 4993-4996.

46. Varma, R. S.; Kumar, D.; Liesen, P. J. Solid state synthesis of 2-aroybenzofuran, thiazoles and 3-aryl-5,6-dihydroimidazo [2,1b] thiazoles using microwave irradiation and α-tosyloxyketones *J. Chem. Soc., Perkin Trans.* **1998**, 1, 4093.

47. Estevam I.H.S.; BiberL.W.; Barbier-type allylation of iminium ions generated in situ in aqueous medium. *Tetrahedron Letters* **2003**, 44, 667-670.
48. Carlos, K. Z.; Andrade. and Luana, M. A. Environmentally Benign Solvents in Organic Synthesis: Current Topics *Current Organic Chemistry* **2005,** *9,* 195-218.
49. Sachdeva, H.; Dwivedi D. and Khaturia, S. Aqua mediated facile synthesis of 2-(5/7-fluorinated-2-oxoindolin-3-ylidene)-N-(4-substituted phenyl) hydrazine carbothioamides. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, **2011**, 213.*
50. Polshettiwar, V.; Varma, R. S. Microwave-assisted organic synthesis using benign reaction media *Accounts of Chemical Research* **2008,** 41 (5), 629-639.
51. Gupta, M.; Paul, S. and Gupta, R. *Review* General Characteristics and Applications of Microwaves in Organic Synthesis Acta *Chim. Slov.* **2009**, *56,* 749–764.
52. Glasnov, T. N.; Kappe, C. O. Continuous-flow syntheses of heterocycles. *Journal of Heterocyclic Chemistry*, **2011** 48 (1), 11-30.
53. Nagendrappa, G. Organic Synthesis Using Clay and Clay-supported Catalysts. Elsevier B. V. **2010.**
54. Caddick, S. Microwave-assisted organic-reactions. *Tetrahedron* **1995**, 51, 10403-10432.
55. Galema, S.A. Microwave chemistry. *Chem. Soc. Rev.* **1997**, 26, 233-238.

Rekha Saroj
Research Scholar

Dr Harshita Sachdeva
Supervisor